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Absence of the Lateral Philtral Ridges: A Clue to the Structural Basis of the Philtrum

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This study compares philtral development in the normal fetus with philtral development in specimens lacking normal philtral landmarks. Distinct differences in the structure of the upper lip were discovered between the two groups using a histological comparison. A new mechanism for the structural basis of the philtrum is proposed on the basis of these differences.

KEY WORDS: philtrum, orbicularis oris, lateral philtral ridges, lip

INTRODUCTION

The unique configuration of the upper lip in humans is largely determined by the philtrum. The external appearance of the philtrum is the result of two structures, the lateral philtral ridges (LPRs) and the midline philtral depression (Fig. 1). Each LPR extends from the lateral aspect of the nasal columella base to the ipsilateral apex of Cupid's bow at the upper lip vermilion border. The philtral depression, located between the two LPRs, extends from the base of the columella to the trough of Cupid's bow at the vermilion midline. Absence of these philtral landmarks results in a smooth upper lip (Fig. 2), a minor malformation often present in the fetal alcohol syndrome and other conditions involving mental retardation. Several investigators have proposed a number of mechanisms for philtral development based on their studies of normal human fetuses but none have analyzed specimens lacking LPRs, particularly with regard to the relationship of a smooth upper lip to abnormal brain development. The purpose of this paper is to present a new hypothesis on development of the philtrum by comparing data obtained from normal human fetuses with that obtained from abnormal human and primate specimens that lack LPRs.

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MATERIALS AND METHODS

To establish normal upper lip anatomy in the developing fetus the upper lips from 32 fetuses varying in gestation from 8 to 21 fetal weeks (by fetal foot length) were used as controls. These fetal specimens were products of conception obtained after therapeutic abortions performed for unwanted but presumably otherwise normal pregnancies. Study specimens were selected for their lack of LPRs. These consisted of seven holoprosencephalic fetuses, one fetus prenatally exposed to alcohol, two fetuses with a bilateral cleft lip, and two normal macaque (monkey) fetuses. The diagnosis and gestational age of each holoprosencephalic fetus are set forth in Table I. They were obtained either as the result of a therapeutic abortion secondary to prenatal diagnosis of the condition or as the result of stillbirth or neonatal death. The fetus exposed to heavy alcohol consumption throughout gestation was aborted spontaneously at 15 weeks. The two macaque fetuses (*Macaca fascicularis*) were normal specimens obtained from the collection of Dr. Andrew Hendrickx from the University of California at Davis. The gestational ages of these fetuses were 48 and 69 days (normal duration of gestation = 155 days). The two fetuses with the bilateral cleft lip, one isolated and one the result of cranial amniotic adhesions, were obtained as the result of therapeutic abortions at 15 and 16 weeks gestation, respectively. The upper lips of all specimens were first fixed in Bouin's solution and then sectioned as illustrated in Figure 3. The sections were embedded in paraffin, cut, mounted, and stained using a routine hematoxylin and eosin technique. Original magnification of all photographs either ×5 or ×8.

RESULTS

Controls

Several important observations were noted in the control group and are set forth in Table II. Macroscopic visualization of LPRs was not detected until 14 fetal weeks. Figure 4a illustrates the lack of LPRs in a 9 week fetus. Orbicularis oris muscle fibers were not detected until week 11 and then gradually increased in density throughout gestation (Fig. 4b–f). Decussation of the orbicularis oris in the midline was first observed at week 15. After decussation, some muscle fibers ap-

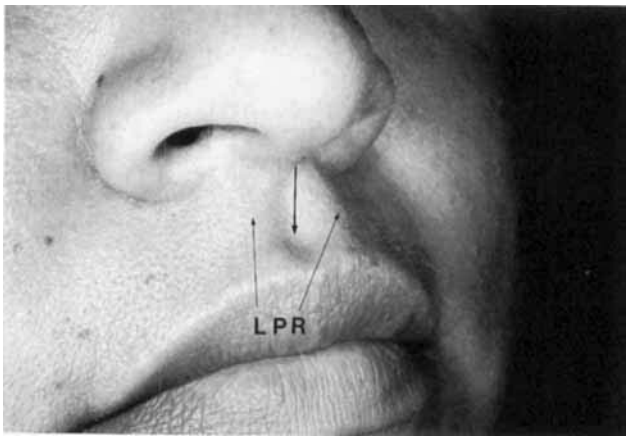

Fig. 1. Normal philtrum with lateral philtral ridges (LPR) and philtral depression (thick arrow).

peared to continue on in a more anterior fashion to insert in the upper lip surface contralateral to their origin (Fig. 4d,e). 11 of 14 specimens at a gestational age of 16 weeks or greater showed some evidence of decussation and anterior insertion. All control specimens except for the 8, 9, and 10 week fetuses had an area of loose connective tissue posterior to the orbicularis oris that was much greater in its volume in the midline than laterally. This connective tissue was at its greatest volume in sections of the lip involving the superior

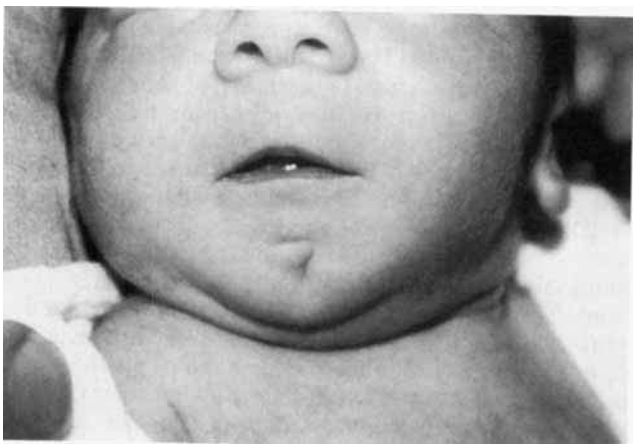

Fig. 2. Smooth upper lip in fetal alcohol syndrome. Note absence of philtral depression and LPRs.

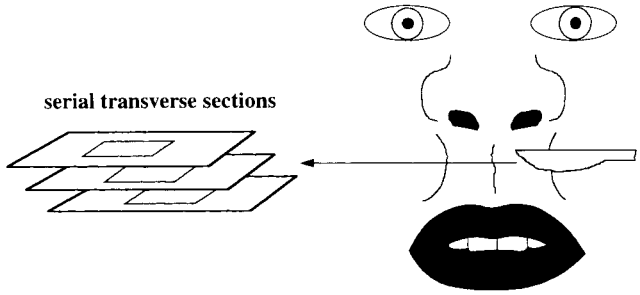

Fig. 3. All specimens were sectioned in this manner.

maxillary frenulum and thus is referred to as frenulum-associated connective tissue (FACT) (Fig. 4). In several specimens the presence of FACT could be appreciated grossly (Fig. 4g).

Specimens Lacking LPRs

1. Holoprosencephaly. None of the histologic landmarks observed in the controls could be seen in any of the holoprosencephalic fetuses (Fig. 5). Upper lip muscle, although present, could not be identified as normal orbicularis oris in any of the seven specimens examined. The upper lip muscle fibers in the holoprosencephaly cases, instead of sweeping across the upper lip in a uniform uninterrupted fashion as seen in the control fetuses, seemed to arise from a number of different planes in a chaotic, disorganized fashion. In addition, all seven specimens were missing FACT.

2. Prenatal alcohol exposure. The upper lip in this specimen was smooth on physical exam. Although the orbicularis oris was present, the normal landmarks observed in the control cases were missing (Fig. 6). The orbicularis oris was thin, lacked decussation and there was no anterior muscle insertion. FACT was also absent.

3. Macaque. The upper lip of the normal macaque is devoid of LPRs (Fig. 7a). FACT was not present in either primate specimen. In the older macaque fetus the orbicularis oris fibers of the upper lip showed no decussation or contralateral insertion but instead plunged posteriorly through the area normally occupied by FACT and appeared to insert directly into the superior labial frenulum (Fig. 7).

4. Prolabium of bilaterally cleft lips. Figure 8a shows the prolabium of a typical isolated bilateral cleft case. Figure 8b illustrates a wide bilateral cleft resulting from cranial amniotic adhesions. Note the absence of LPRs in both cases. Sections from both specimens

TABLE I. Holoprosencephaly Specimens

Case	Diagnosis	Type	Face	Gestation (weeks)
1	Isolated	Alobar	Hypotelorism	38
2	Trisomy 13	Alobar	Cyclopia	18
3	Isolated	Alobar	Cebocephaly	21
4	Trisomy 13	Alobar	Cebocephaly	17
5	Isolated	Alobar	Cyclopia,otocephaly	Unknown
6	Isolated	Unknown	Cyclopia	20
7	Isolated	Unknown	Hypotelorism	20

TABLE II. Upper Lip Findings in Fetal Control Specimens

N	Gestation (weeks)	Philtral ridges	Orbicularis oris	Decussation	FACT
1	8	Absent	Absent	None	Absent
1	9	Absent	Absent	None	Absent
1	10	Absent	Absent	None	Absent
1	11	Absent	Present	None	Present
1	12	Absent	Present	None	Present
3	13	Absent	Present	None	Present
3	14	Absent	Present	None	Present
3	14	Present	Present	None	Present
4	15	Present	Present	1 of 4 cases	Present
3	16	Present	Present	2 of 3 cases	Present
3	17	Present	Present	2 of 3 cases	Present
2	18	Present	Present	2 of 2 cases	Present
3	19	Present	Present	2 of 3 cases	Present
2	20	Present	Present	2 of 2 cases	Present
1	21	Present	Present	1 of 1 case	Present

demonstrate absence of orbicularis oris muscle despite the presence of FACT (Fig. 8c and 8d).

DISCUSSION

These data suggest that LPRs develop as a result of interaction between the orbicularis oris muscle, a derivative of the maxillary process, and frenulum-associated connective tissue (FACT), a derivative of the medial nasal process. Evidence in support of this conclusion is as follows.

LPRs were not present until 14 weeks of gestation, a finding previously reported by others [Monie and Cacciatore, 1962; Lee, 1988]. Because upper lip formation is complete by week 7 [O'Rahilly and Müller, 1992] this finding negates the possibility that LPRs are the result of facial process fusion or merging events. The delayed appearance of LPRs suggests that the mechanism of their formation is related to a later embryonic event. The absence of orbicularis oris muscle fibers prior to week 11 suggests that this later event is orbicularis oris muscle development. The orbicularis oris muscle is derived from mesoderm of the second branchial arch that migrates medially to form the maxillary processes [Fara and Smahel, 1967]. After week 11 there is a gradual increase in orbicularis oris muscle fiber density as gestational age increases (Fig. 4). At week 15–16 orbicularis oris muscle fibers from each lateral aspect of the lip course towards the midline where they decussate and continue on to an eventual insertion anteriorly into the surface skin of the lip contralateral to their origin leaving the midline free of any muscle insertion (Fig. 4). This phenomenon was observed in 11 of 14 specimens 16 weeks or greater in gestation. Latham and Deaton [1976] also described a similar pattern of decussation and anterior fiber insertion beginning at 14 weeks gestation. The lack of this phenomenon in all specimens 14 weeks or greater in this study is likely a result of using single sections rather than the plexiglass sheet reconstruction method used by Latham and Deaton which allows observation of more individual fibers. The first observation of LPRs at 14 weeks gestation in this study correlates with the phenomenon of orbicularis oris fiber decussation and anterior lip insertion and suggests that these late embryonic events result in formation of LPRs, a conclusion also reached by Latham and Deaton. Lee [1988] documented a similar muscle configuration but he postulated that LPR formation was secondary to the dynamic process of orbicularis oris contraction and relaxation rather than the muscular insertion itself. However, there are some disorders (eg Möbius sequence and congenital myotonic dystrophy) where facial muscle movement is minimal but LPRs are nonetheless present making Lee's supposition untenable.

All control specimens after 10 weeks gestation in this study had a connective tissue prominence in the midline posterior to the orbicularis oris that has not been previously described (Figs. 4c–f). In some cases this prominence was visible macroscopically as well (Fig. 4g). This connective tissue prominence appeared to be associated with the superior labial frenulum and thus was labeled frenulum-associated connective tissue (FACT).

That the orbicularis oris muscle and FACT contribute to normal philtral development is only suggested by the observations in the control specimens but their importance in this regard is clearly demonstrated when lip sections of the study group are compared to the control group. Three of the study specimen groups (holoprosencephaly, alcohol exposure and the macaque) differed from the controls beyond their lack of LPRs in three ways: 1) all lack FACT, 2) all have abnormalities of the orbicularis oris muscle, and 3) all have alterations of forebrain development as compared to the controls. The forebrain plays a significant role in the development of the midline portion of the upper lip, primarily through neural crest cell derived mesoderm which forms the medial nasal process (MNP). Holoprosencephaly is a defect of forebrain development resulting in deficiency of the medial nasal process and a cadre of midline lip abnormalities including absent LPRs. Sulik et al. [1981] demonstrated that prenatal ethanol exposure severely compromised forebrain and MNP development in mice. They suggested that the fa-

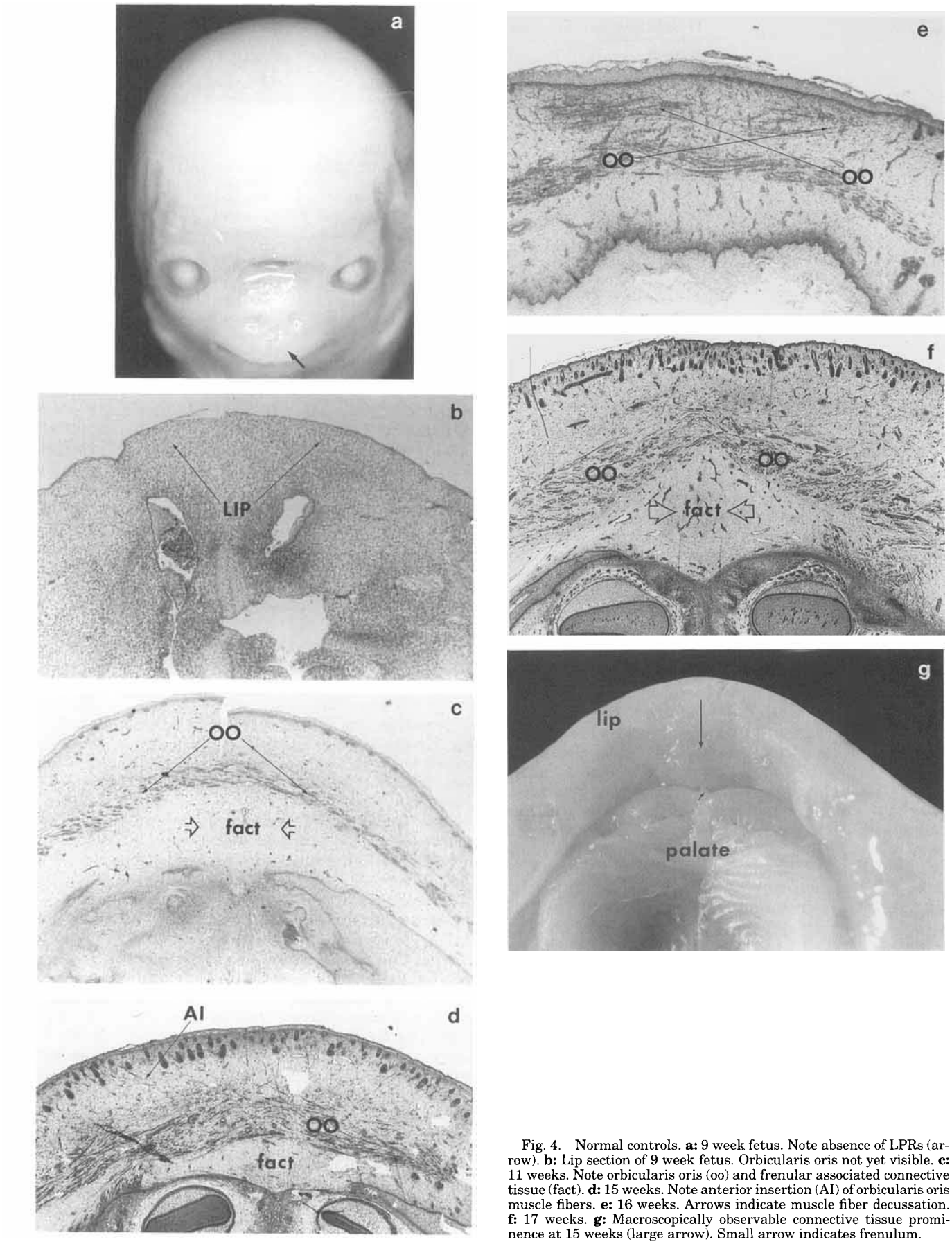

Fig. 4. Normal controls. **a:** 9 week fetus. Note absence of LPRs (arrow). **b:** Lip section of 9 week fetus. Orbicularis oris not yet visible. **c:** 11 weeks. Note orbicularis oris (oo) and frenular associated connective tissue (fact). **d:** 15 weeks. Note anterior insertion (AI) of orbicularis oris muscle fibers. **e:** 16 weeks. Arrows indicate muscle fiber decussation. **f:** 17 weeks. **g:** Macroscopically observable connective tissue prominence at 15 weeks (large arrow). Small arrow indicates frenulum.

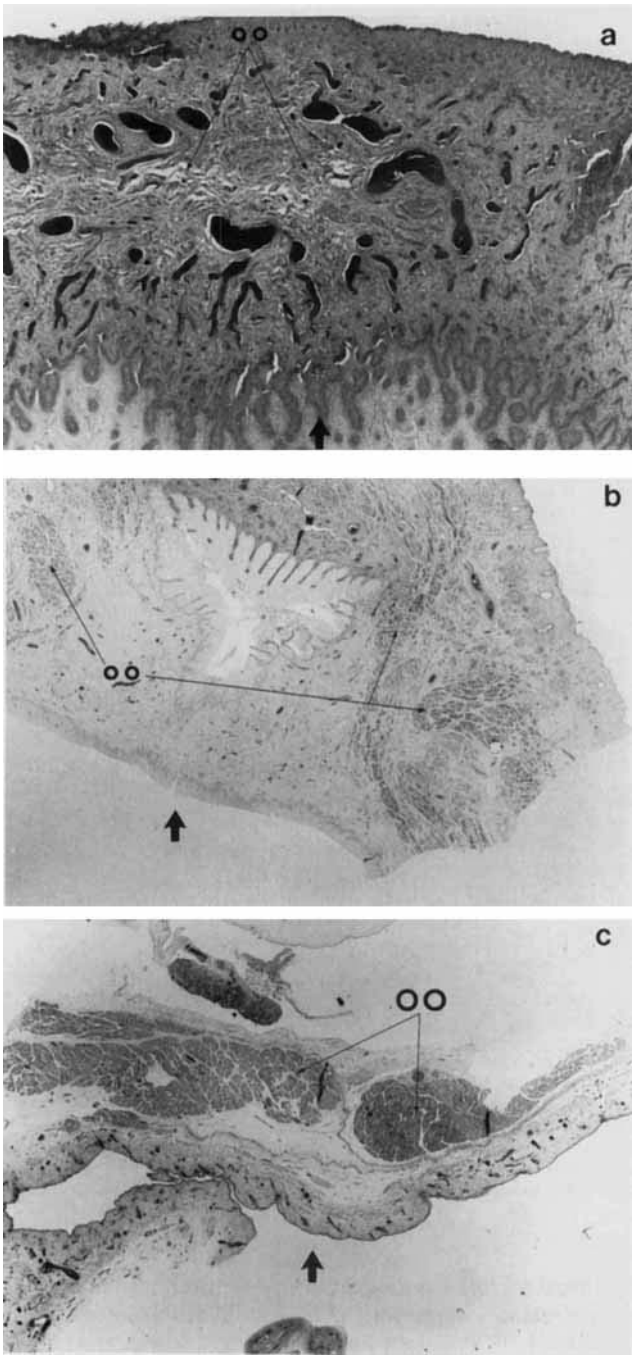

Fig. 5. Holoprosencephaly. Thick arrow denotes lip midline. Note abberant muscle pattern of orbicularis oris (oo) and absence of FACT. (**a**), case 1; (**b**), case 5; **c**, case 6.

cial anomalies (including smooth upper lip) of fetal alcohol syndrome in humans are explained by this compromise. In the macaque specimens lacking LPRs, forebrain development is significantly reduced compared to humans [Napier and Napier, 1967] so a significant reduction in MNP contribution to the upper lip is expected.

FACT presence in the upper lip midline of controls and its absence in specimens with forebrain deficien-

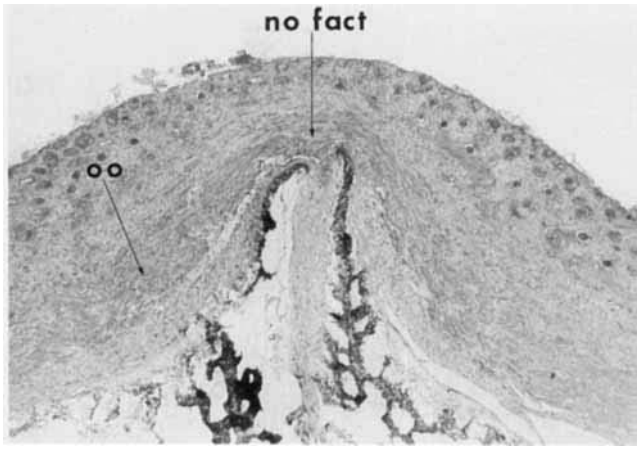

Fig. 6. Heavy prenatal alcohol exposure. Note thin orbicularis oris (oo), absence of decussation and absence of FACT.

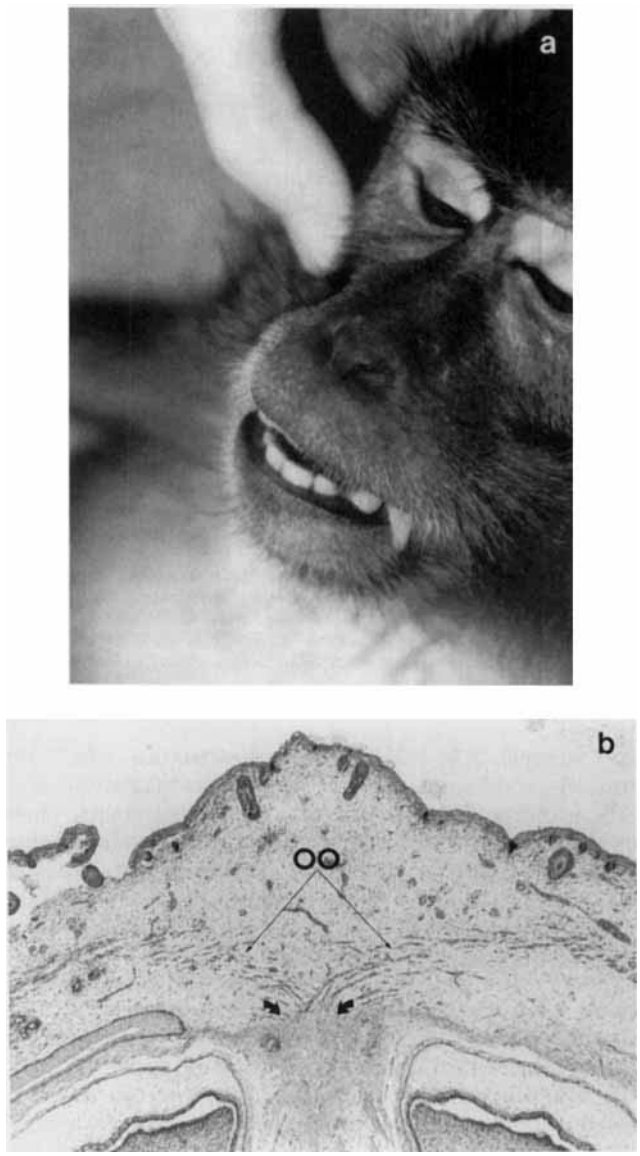

Fig. 7. Macaque. **a:** Note smooth upper lip. **b:** Note absence of FACT and posterior direction of orbicularis oris insertion (oo) into frenulum (thick arrows).

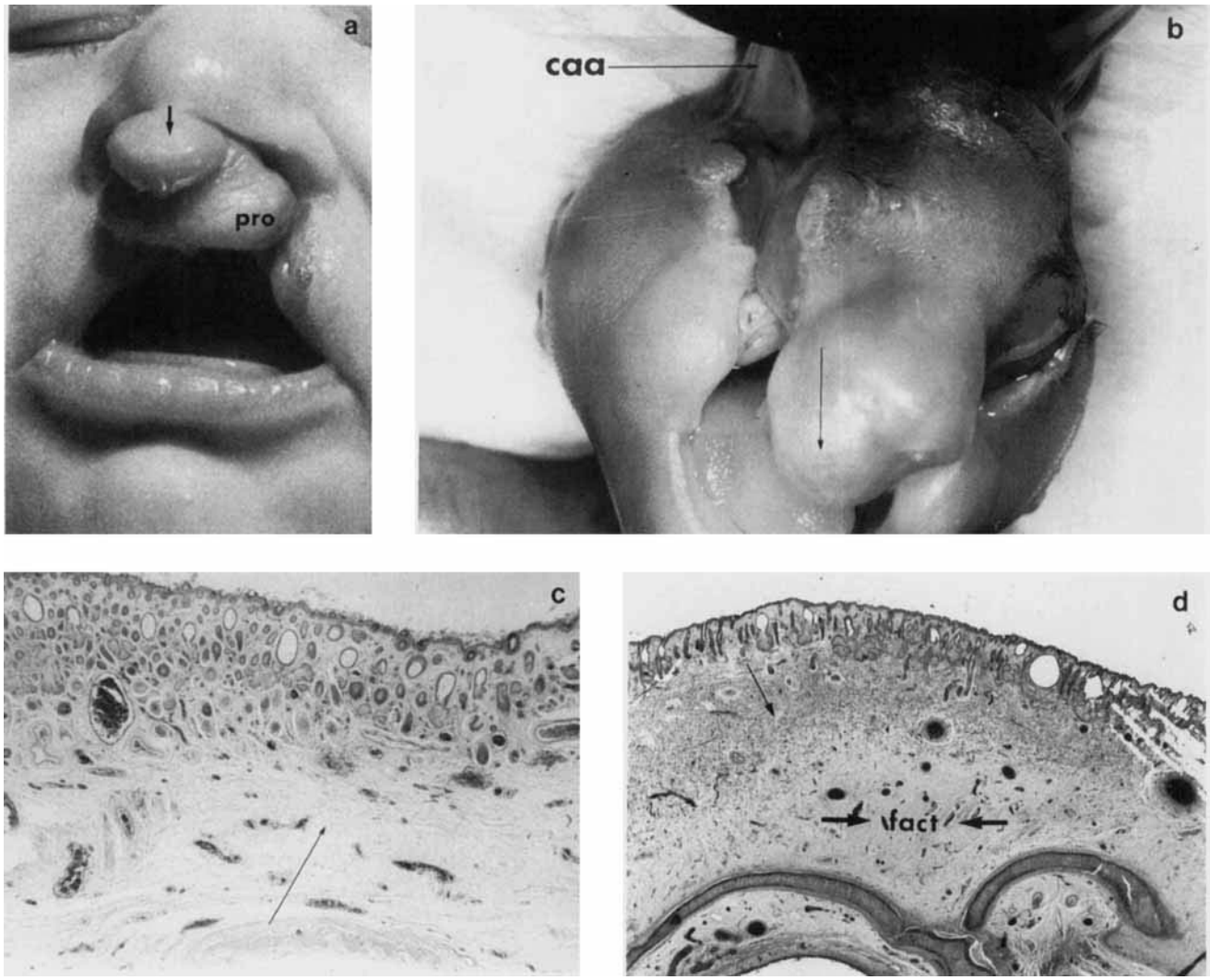

Fig. 8. Bilateral cleft lip. **a:** Prolabium (pro) of typical isolated bilateral cleft. Note absence of LPRs on lip of prolabium (arrow). **b:** Bilateral cleft secondary to cranial amniotic adhesion (caa). Arrow indicates prolabium. Note wide lateral clefts and absent LPRs (photo courtesy of Dr. Robin Clark). **c:** Section taken from lip similar to a. Arrow indicates absence of orbicularis oris fibers. **d:** Section taken from lip similar to c. Single arrow indicates absence of orbicularis oris despite presence of FACT.

cies suggest it is a MNP derived structure. FACT absence in specimens without LPRs also suggests that it is a primary determinant of LPR development. However, since FACT absence in this study was also always associated with an abnormal orbicularis oris, its primary role may be to guide normal orbicularis oris development rather than acting directly on LPR formation. The analysis of bilaterally cleft lips in this study supports this possible relationship. The bilateral cleft cases were the only study specimens having FACT in the absence of LPRs. In a bilateral cleft lip the normal mesoderm contribution to the midline upper lip from the maxillary processes cannot occur across the cleft space. The result is a midline lip remnant, known as the prolabium (Fig. 8a), that is derived solely from the MNP [Millard, 1977] and so lacks orbicularis oris muscle (Fig. 8c). LPRs are not present in the prolabium of a bilaterally cleft lip despite a presumably normal MNP contribution suggesting that FACT alone is not sufficient for LPR development. One might argue that LPRs are not observed in the bilateral cleft lip simply because the cleft would obliterate them. However, LPRs are also absent in bilateral clefts of the lip that occur lateral to the typical area of clefting such as seen in specimens with clefts secondary to cranial amniotic adhesions (Fig. 8b,d). The mechanism of cleft production in this specimen has allowed a normal contribution of MNP (and FACT) to the upper lip but impeded maxillary process mesoderm from migrating medially to form the orbicularis oris. This case demonstrates that absence of LPRs in bilateral cleft lips is unrelated to the location of the cleft. The pathogenesis of the isolated bilateral cleft and the cleft created by cranial amniotic adhesions is quite distinct yet the result is the same – loss of max-

illary mesoderm contribution to the MNP derived midline remnant of the upper lip. These data indicate that FACT alone does not induce LPR formation but that maxillary process mesoderm contribution, presumably through the orbicularis oris, is also required.

In summary, the data presented in this study confirm prior investigations that suggest the orbicularis oris muscle plays an important role in LPR development. However, new data based on specimens lacking LPRs clearly demonstrate that presence of the orbicularis oris muscle alone is not sufficient for normal philtral formation. Without FACT a normal orbicularis oris does not develop. FACT appears to interact with the orbicularis oris muscle in such a way as to direct its insertion anteriorly into the upper lip leading to the normal configuration of the LPRs. If this hypothesis is correct, it demonstrates temporal regulation of facial development exerted by one facial process (MNP) on another (maxillary) since FACT is in place before orbicularis oris muscle formation begins. From a clinical perspective, a smooth upper lip in a child should raise concern that this MNP regulatory effect did not occur as a consequence of an underlying defect in forebrain development.

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